UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,869	07/06/2001	Stuart J. Knechtle	14028.0293U1	1262

23859 7590 03/29/2005

NEEDLE & ROSENBERG, P.C.
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,869	KNECHTLE ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *14-20 and 29-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

1. Applicant's amendment, filed has been entered.
Claims 1 and 7-9 have been amended.

2. Applicant's election with traverse Group I and the provisional election of species (i) CTLA4-Ig and amendment to the claims to recite anti-CD3 immuntoxin is acknowledged.

Applicant traverse the Restriction Requirement on the grounds that the inventions must be both independent and distinct and an undue search burden on the examiner. However, MPEP 803 states that the Inventions be either independent or distinct and a burden on the Examiner if restriction is required.

Regarding applicant's comments about undue burden, the MPEP 803 states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the examiner by the examination Groups. The Inventions are distinct for reasons elaborated in the previous Office Action.

As pointed out previously in the Restriction Requirement, should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

It is noted that prosecuting the elected species is in the interest of compact prosecution, given the prior art rejection set forth herein and the search burden on addressing the number of species encompassed by the claims.

In addition, it is not clear that applicant traverses between Groups I and II set forth in the previous Restriction Requirement.
Should applicant traverse on the ground that the Groups are not patentably distinct, then applicant is invited to point out the prior art support for the disclosure on page 10, paragraph 1, of the instant specification with respect to the "histological and clinical signs of acute rejection".

Claims 1-13 and 21-28 are being examined to the extent that the methods reads on methods of preventing chronic rejection of a transplant by administering anti-CD3 immunotoxin and CTLA4.

Claims 14-20 and 29-33 have been withdrawn from consideration as being drawn to non-elected Groups or species.

3. The Title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. This application does not contain an Abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6. The filing date of the instant claims is deemed to be the filing date of priority application USSN 60/115,252.

However, an incorporation-by-reference statement added after the filing date of an application is not permitted because no new matter can be added to an application after its filing date. See 35 USC 132(a).

Also, see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) (see Part VII).

Applicant should amend the Preliminary Amendment, filed 1/8/02, by deleting the following: "which applications are hereby incorporated herein in their entirety by reference".

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

It is apparent that the UCHT1-CRM9 immunotoxin is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line which produces this immunotoxin. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Alternatively, applicant is invited to provide evidence that the conditions required for the biological materials under the deposit requirements under 35 USC 112, first paragraph, with respect to the claimed "UCHT1-CRM9 immunotoxin" have been satisfied.

9. Claim 10 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite in the recitation of "UCHT1-CRM9" because its characteristics are not known. The use of "UCHT1-CRM9" immunotoxin as the sole means of identifying the claimed antibody and biological molecule renders the claim indefinite because "UCHT1-CRM9" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct biological materials or cell lines.

Amending the claims to recite the appropriate deposit Accession Number would obviate this rejection.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

10. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-13 and 21-28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Neville et al. (U.S. Patent No. 6,103,235) in view of Sykes et al. U.S. Patent No. 6,514,513) AND/OR Gray et al. (U.S. Patent No. 6,750,334) and in further view of Strom et al. (in Therapeutic Immunology, edited by Austen et al., Blackwell Science, Cambridge MA, 1996; pages 451-456).

Neville et al. teach methods of inducing immune tolerance or immunological specific non-responsiveness to foreign mammalian donor organs cell (e.g. including live donors on column 8, paragraph 2 and column 9)

by safely exposing the recipient so as to reduce the recipient T cells with anti-CD3 immunotoxins, including the UCHT1-CRM9 / T cell CD3ε epitope –specific / divalent / diphtheria (e.g., see columns 4-10 of the Detailed Description of the Invention),

including administering known immunosuppressant such as those encompassed by the instant claims (e.g. see Method of Inducing Immune Tolerance, Methods of Treating Graft –Versus-Host Disease on columns 8-10, particularly column 8, paragraph 5 – column 9) (see entire document).

Neville et al. also teach modes of administering, including administering said immunotoxin prior to, during and following transplantation, wherein one skilled in the art can readily determine the particular treatment protocol and suitable amounts (e.g., see column 7, paragraph 2 – column 10).

Such methods present a significant opportunity to reduce or eliminate traditional immunosuppressant therapy and its well -documented negative side-effects (e.g. see column 9, paragraph 1).

Neville et al. differs from the instant methods by not describing the known costimulatory blockers such as CTLA4 / CTLA4-Ig in immunosuppressive regimens to promote graft survival.

Sykes teaches methods of inducing tolerance to foreign antigens, including heart, pancreas, liver and kidney (e.g. see column 8, paragraph 2) by promoting primate / human allograft acceptance by administering a costimulatory blocker, including CTLAIg (e.g. see column 9, paragraph 2-3)

including combination with T cell depletion or inactivation with anti-T cell antibodies (e.g. see column 9, paragraphs 6-8 and column 13, paragraphs 2-6).

Similar to Neville et al., Sykes teaches various modes of administration including providing immunosuppressive therapy multiple times prior to, during and after transplantation according to the needs of the patients (see Detailed Description).

Sykes differs from the instant methods by not describing the anti-CD3 immunotoxins encompassed by the claimed methods.

Gray et al. teach the use of CTLA-4 Ig fusion proteins for downregulating immune responses by inducing non-responsiveness (or tolerance or anergy), including in human transplantation (e.g. heart, liver, kidney) on column 21, paragraph 1),

including in combination with agents that inhibit T cells or induce general immunosuppression such as cyclosporine or FK506 (e.g. see columns 22, paragraphs 1-2) (see entire document, including Uses of CTLA4-Immunoglobulin Fusion Proteins Having Reduced IgG Region-Mediated Biological Effector Functions on columns 21-23).

Here, treatment can occur prior, during and post transplantation is described and therapeutic dosing regimens can be adjusted to provide the optimum therapeutic responses (see Compositions of CTLA4-Immunoglobulin Fusion Proteins on columns 19-21).

Gray et al. and Sykes differ from the instant methods by not describing the anti-CD3 immunotoxins as a means to reduce or inhibit T cell responses in transplantation immunosuppressive regimens, encompassed by the claimed methods.

In describing therapeutic approaches to organ transplantation, (see entire document), Strom note the known multi-tiered approach to immunosuppressive therapy in that several agents are used simultaneously, each of which is reacted at a different molecular target within the graft response and achieving additive-synergistic effects through application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agents while increasing the total immunosuppressive effects (see page 451, column 1, paragraph 1). Strom concludes by anticipating that in the near future, antibodies and fusion proteins that target discrete steps in antigen recognition, signal transduction and effector immunity will be applied clinically.

The prior art is consistent with the known multi-tiered approach of targeting discrete steps in antigen recognition, signal transduction and effector immunity taught by the referenced methods of administering anti-CD3 immunotoxins (e.g., claims 6-10) and/or CTLA4Ig (e.g., claims 21-22) in combination with traditional or standard immunosuppressive therapy (e.g., claims 23-26, 27-28) associated with preventing chronic rejection of a transplant (e.g., claims 2-5, 11-13).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of the references to reduce or eliminate T cell responses via a multitiered approach by combining anti-T cell immunotherapy, such as the anti-CD3 immuntoxins, taught by Neville et al., with a costimulatory inhibitor such as CTLA4Ig, as taught by Sykes and Gray et al., in order to target different targets and mechanisms of action to increase immunosuppresssion while decreasing the undesirable effects of immunosuppression therapy, including that which accompanies transplantation. As pointed out above, each of the references describe the known use of combination therapy, including combination therapy that targets T cells and eliminates or reduces the number or the function of T cells in combination with other immunosuppressive agents that have different targets and mechanisms of actions associated with achieving the desired immunosuppression and promotion of long term graft survival. As pointed out above, the references describe the use of either anti-CD3 immunotoxins or CTLA4 immunosuppressive agents in terms consistent with the advantages of the combination therapy of addressing different targets and mechanisms of action in efforts to increase safety and to decrease known toxic or side-effects of immunosuppression regimens at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

For examination purposes, "a method of preventing chronic rejection of a transplant" is read on broadly encompassing preventing the clinical signs and symptoms disclosed on pages 5-6 of the instant specification by administering effective amounts of antagonistic anti-CD3 immunotoxins and CTLA4 consistent with standard or traditional modes of transplantation immunosuppressive recognized and practiced by the ordinary artisan regimens at the time the invention was made.

Here, the prior art teaches and the instant methods encompass
the same patient populations who are being treated with same immunosuppressive regimens to achieve the same clinical endpoints at the same intervals based upon the needs of the patient,
whether or not the patients necessarily experienced long term immunological non-responsiveness or tolerance.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
March 14, 2005